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THE USE OF MERCURIAL DIURETICS IN CONGESTIVE HEART FAILURE*

The importance of diuretic agents in the management of congestive heart failure is well established. Among these the organic mercurials are considered the most potent, most dependable, and most rapidly acting drugs.

FUNDAMENTALS OF MERCURIAL DIURESIS

An understanding of the basic pharmacology of the mercurial diuretics is indispensable in employing them with optimum results and in avoiding side effects.

The diuretic action of a single dose of a mercurial compound is based upon the entry of ionized mercury into the tubular epithelial cells. At this site the mercury exerts an inhibitory action upon the enzymes concerned with the reabsorption of electrolytes from the glomerular filtrate. Since this action largely depends on a sufficiently high concentration of mercury in the tubular epithelium, prompt passage of the mercury from the site of injection into the blood stream and its rapid excretion through the kidneys are equally important. On the other hand, *complete* elimination of the mercury within a reasonable period is necessary to avoid the effects of cumulation in the system. The organic mercurial compounds can fulfill these postulates if injected intravenously, intramuscularly, or subcutaneously (into edema-free areas) at appropriate intervals. The advisability of spacing mercurial injections at not less than 48-hour intervals is based on the following experience: Only under favorable circumstances, i.e., with good renal function and ample diuresis, is a therapeutic dose of mercury (40 to 80 mgm., as contained in 1 to 2 cc. of the commercial preparations) excreted within 24 hours. Frequently, however, only 40-60 per cent of the mercury is eliminated in the urine during the first day, and 3 to 8 days may elapse before all the mercury is excreted.

The depressant effect of mercury upon the function of the tubular cells consists in blocking the reabsorption of (1) chloride — primary and chief effect (2) sodium — as a chemical collateral to the rejection of chloride, and (3) water — as an osmotic consequence of the high concentration of sodium chloride in the tubular urine. The loss of body fluid leads to an immediate reduction in the circulating blood volume at the expense of plasma, i.e., hemoconcentration. This, in turn, causes tissue fluid to shift into the circulation until the plasma volume is partly restored. The net result of an effective diuresis in any individual is a fall in extracellular fluid volume (interstitial fluid plus blood plasma). When body fluid has been present in excess, the final therapeutic result of diuresis is disappearance of edema and return of the blood volume to normal. The functional improvement in circulation is derived essentially from a combination of: (1) increased cardiac output (due to the reduction in total blood volume and the redistribution of blood in formerly obliterated venous and capillary spaces), (2) improved respiration (due to reduced edema in the pulmonary parenchyma and a decrease in pleural effusions and hepatic congestion, resulting in a restored pulmonary gas exchange and more effective ventilation), and (3) diminished body weight.

It is during this phase of circulatory readjustment, when edema and serosal effusions begin to subside, that subjective improvement becomes apparent.

SIDE EFFECTS OF MERCURIAL DIURETICS

In order to plan a rational diuretic regimen with mercurials, it is well to review their many possible side effects. The incidence of side reactions has increased with the more liberal use of mercurials and the growing popularity of salt-free diets. These reactions can be divided into three major groups: (1) Those from a single excessive dose or from cumulation of mercury (acute or chronic mercury poisoning); (2) those due to hypersensitivity to either mercury as such or to a specific compound; (3) those produced by excessive diuresis, such as dehydration, electrolyte depletion, "spontaneous redigitalization," or acute urine retention.

Mercury Poisoning

Acute poisoning has resulted from attempts to overcome a failing response by using up to 6 or 8 cc. of a commercial preparation in a single dose. Such a practice is unwise because of the danger involved (6 cc. has been calculated to be the maximum non-lethal dose in man). It is also

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futile. Inhibition of tubular reabsorption has been found to be maximum with a 2 cc. dose and cannot be intensified by larger doses.

Electrocardiographic evidence of minor acute myocardial injury following *intravenous* injection has been demonstrated in about 10 per cent of individuals. Serious reactions of this type are rare. They range from multiple premature ventricular contractions to ventricular tachycardia and fatal ventricular flutter or fibrillation. Fatalities of this type have been observed particularly in patients with nephrotic edema. The intravenous route should therefore be avoided in general but particularly in patients who have previously shown some cardiac arrhythmia after mercurial injections and in patients with renal edema.

Subacute or chronic mercurialism with stomatitis, hemorrhagic colitis, or severe toxic nephrosis have occurred with attempts to force a diuretic response by daily or even twice a day injections of 2 cc. or more. Patients with pre-existent renal disease are apparently predisposed to such complications. They may be saved by the prompt use of BAL. Side effects of this type can be avoided by the proper spacing of injections with due consideration to the renal status and the diuretic response. With these precautions, patients have received hundreds of mercurial injections in the course of years without any clinically or histologically demonstrable injury to the kidneys.

Allergic Reactions

Reactions of hypersensitivity to mercurials are not common and are of little consequence if recognized early. They develop almost invariably after the prolonged use of a single drug. Following intravenous injection, the symptoms appear immediately while they are somewhat delayed following intramuscular or subcutaneous administration. Symptoms are usually mild in the beginning and consist in chilliness, fever, cutaneous eruptions, or vomiting. They become increasingly severe with every subsequent injection. Finally, shaking chills, hyperpyrexia, substernal oppression, air hunger, and cardiac arrhythmias may occur and can terminate in irreversible shock and death.

Serious accidents of this type can be eliminated, if, as a matter of routine, the intravenous use is avoided and the patient is questioned about previously experienced reactions before the next injection is given. Occasionally continuation of treatment with the same mercurial preparation may be possible if the route of administration is changed or antihistaminics are simultaneously administered. However, since hypersensitivity is usually limited to one specific compound, it is best to change preparations. Before a full dose of the newly selected compound is given, the patient's sensitivity should be tested by hypodermic injection of a small quantity (0.05 to 0.1 cc.).

An extremely rare allergic manifestation is agranulocytosis. It is related to sensitivity to a specific compound, is reversible if recognized early, and does not recur if a different preparation is used subsequently.

Effects of Excessive Diuresis

A definition of "excessive diuresis" in terms of urine volume alone is difficult if not impossible. It is the undesirable sequelae which change a diuretic response from "copious" into "excessive." In general, however, a 24-hour weight loss of not more than 10 pounds in a grossly edematous and 5 pounds in a moderately edematous patient can be regarded as safe.

(a) *Hemoconcentration:* Rapid and profuse diuresis can lead to a serious degree of hemoconcentration and a corresponding rise in blood viscosity, especially when the diuresis is accompanied by a restricted fluid intake or by fluid loss through vomiting, diarrhea, or excessive perspiration. The condition is reflected by an elevated hematocrit and, clinically, by prostration, weak pulse, fall in blood pressure. It may, mainly in elderly people, lead to serious impairment of the cerebral circulation or to coronary, cerebral, or peripheral thrombus formation. Injurious degrees of dehydration can be avoided by keeping the dose of the mercurial as small as possible (particularly in the aged and debilitated) and by supplying water liberally, if need be by vein or stomach tube.

(b) *Electrolyte Depletion:* Following liberal use of mercurials, disturbances of electrolyte balance are more likely to occur in patients whose dietary salt intake is very low. Under such circumstances electrolyte depletions of the following kind are not rarely encountered: (1) a proportionate *reduction in serum sodium and chloride concentrations*, e.g., 120 mEq/L of sodium (normal: 140) and 86 mEq/L of chloride (normal: 100) and (2) a predominant *chloride deficiency*, e.g., 135 mEq/L of sodium and 86 mEq/L of chloride. Both types of electrolyte depletion lead to azotemia and are symptomatically very similar. The clinical picture of this "low salt syndrome" combines, as a rule, striking weakness, anorexia, nausea, drowsiness, or restlessness and confusion with a rapidly increasing refractoriness to mercurial diuretics.

For a rational management it is important to differentiate the two types by measurement of Na, Cl, K, Urea-N, and CO_2 combining power in the blood. In the event of uniform sodium and chloride deficiency, the slow intravenous infusion of a 5 per cent NaCl solution (not more than 200 cc. at a time) can, at an early stage, correct the electrolyte imbalance with the result that a subsequent mercurial injection may be followed by a good diuresis. On the other hand, in case of chloride deficiency (hypochloremic alkalosis) the infusion of a 1 per cent ammonium chloride infusion in 5 per cent glucose is indicated. Not more than 200 cc. must be administered per hour to

avoid liberation of ammonia in toxic concentrations.

The presence of *potassium deficiency* is suggested clinically by the occurrence of a striking degree of muscular weakness and of cardiac irregularities; the diagnosis can be ascertained by serum potassium determination and often also by the electrocardiogram.[5] Since potassium depletion increases myocardial excitability, it may partly (or possibly entirely) be responsible for the so-called "spontaneous redigitalization" in the course of massive diuresis, a phenomenon which in the past has been ascribed to the mobilization of digitalis from depots in the tissue fluids. Oral administration of potassium salts in doses of 3.0 to 6.0 gm. will in most cases be sufficient to abolish this disturbance.

Prompt recognition and correction of these syndromes is important. Their prevention depends on avoidance of excessive diuresis, by individualization of salt restriction, and by close attention to the electrolyte status. These precautions are indispensable whenever prolonged mercurial treatment is required in an older patient, in advanced congestive failure, in the presence of known or suspected renal insufficiency, or in patients who had been on a rigorous or an unknown dietary and diuretic regime.

Acute urine retention may develop without warning in elderly bedridden males at the onset of copious diuresis. This happens more often in patients who are under sedation or unable to stand for voiding. Prompt catherization is required.

INDICATIONS

Mercurial diuretic injections are indicated:

(1) In chronic congestive heart failure which cannot be adequately controlled by rest, digitalization, sodium restriction, or, possibly, by oral, non-mercurial diuretics, no matter whether the excess fluid is present in the form of visible edema or of pulmonary or hepatic congestion.

(2) As a preventive measure in recurrent left ventricular failure (with paroxysmal nocturnal dyspnea or pulmonary edema) as soon as a rise in the weight curve suggests the imminence of another attack.

(3) In congestive failure due to a myocardial disease which responds poorly or not at all to digitalis, such as active myocarditis, uncontrollable tachycardia, or cor pulmonale.

(4) In systemic venous congestion due to inflow stasis resulting from mechanical obstruction, such as tricuspid stenosis, constrictive pericarditis, pericardial effusion, or tight mitral stenosis with regular cardiac rhythm.

(5) For therapeutic testing, such as for (a) the differentiation of passive pulmonary congestion from bronchitis and bronchiectasis, (b) the differentiation of "cardiac asthma" from bronchial asthma, (c) the differentiation of dyspnea on effort from angina on effort. Prompt — even though transient — improvement following satisfactory diuresis points to left ventricular insufficiency as the cause of the symptoms.

ORGANIC MERCURIAL PREPARATIONS

Most of the organic mercurial preparations available for parenteral use, such as Mercuhydrin®, Mercuzanthin®, Salyrgan-Theophylline®, and Cumertilin®, contain about 40 mgm. of mercury per cc. and 30 to 50 mgm. of theophylline. Their absorption from an intramuscular depot is prompt, and they are, in general, equally effective. They are administered by vein or, preferably, intramuscularly.[6]

Thiomerin®, which contains a mercaptan instead of theophylline, and Dicurin Procaine® can be employed subcutaneously.[1]

The rectal route is not favored because of unpredictable absorption and frequent rectal irritation from mercurial suppositories.

The oral use of mercurial diuretics has been accepted with some reluctance. Its effect is uncertain and the symptoms of mercurialism such as metallic taste, nausea, epigastric distress, abdominal griping, gingivitis, and colitis are frequent. Only 5-10 per cent of the ingested mercury has been found to be absorbed and excreted in the urine. Neohydrin® and Cumertillin®[4] are effective in doses of less than 4 tablets daily (corresponding to 40 to 48 mgm. of Hg, respectively) as compared with other preparations which require a dosage corresponding to not less than 75 to 180 mgm. of mercury per day. No adequate comparative studies however are available in the literature as to the merits of the various oral preparations.

PLAN OF DIURETIC TREATMENT WITH MERCURIALS

The following rules based upon our present knowledge of the physiology and pharmacology of mercurial diuresis may serve as guidance in the use of the mercurials:

1. The use of these potent drugs should be limited to situations in which other methods of treating congestive failure have not succeeded or cannot be expected to achieve the desired goal rapidly enough.

2. Only a small initial dose should be employed; subsequent dosage depends upon the effects of the preceding dose and upon the rate of reaccumulation of edema.

3. The intervals between single injections should be long enough to ensure almost complete excretion of the mercury and reestablishment of renal tubular function and electrolyte balance.

4. One should never exceed the dose of 1 to 2 cc. in any single injection, nor administer those doses without interruption on successive days. A series of injections should never be scheduled in advance since these might be continued longer than needed or after serious complications have developed.

5. In resistant cases one should combine mer-

curials with diuretic drugs of different pharmacologic mechanism rather than increase the dosage of the mercurial.

6. Symptoms of hypersensitivity must be watched for, and the particular mercurial compound which has produced such symptoms should be permanently discontinued. Extreme caution is required when a different mercurial compound is substituted for the one which caused reactions.

7. The intramuscular or subcutaneous route is preferred to intravenous injections. The latter should be restricted to the use of mercurials in combination with some other preparations, such as aminophylline or decholin. They should only be given to patients who have shown no evidence of hypersensitivity to preceding intramuscular administration.

The following procedure is recommended[7]: In moderately severe congestive failure mercurial diuretics are started as soon as other measures prove inadequate; whereas in patients with severe distress due to advanced congestive failure a mercurial injection is administered without delay and without waiting for the effects of full digitalization. The first dose usually does not exceed 1 cc. in adults and 0.5 cc. in children and very small adults. In patients with marked edema who are expected to require prolonged mercurial treatment, serum Na, Cl, CO_2 combining power and Urea-N are determined at the outset. If, following the first injection, the diuresis is sufficient but edema is still present, the same dose is administered two or three days later. If, however, the diuresis is inadequate, the dose is increased to 1.5 to 2 cc., but may have to be reduced again if diuresis tends to become excessive. This procedure is continued until optimum improvement of the subjective and objective manifestations of congestive failure has been achieved. The goal is maintenance of the "basal weight level." Injections are not continued to a point at which they produce no more weight reduction (actual "dry weight") since this would represent an undesirable state of dehydration.

If, however, no progress is made and the patient appears to be "refractory" to mercury, the administration of mercurials is discontinued pending a thorough re-evaluation of the situation. This must include: reassessment of the diagnosis (such as ruling out hyperthyroidism, pulmonary embolism, pericardial constriction, hepatic cirrhosis, renal insufficiency); elimination of antidiuretic agents (such as narcotics, sodium containing food or drugs, or excessive fluid restriction); adjustment of digitalis (to ensure against suboptimum digitalis medication or possible digitalis toxicity); and serum electrolyte estimations (to detect possible electrolyte depletion, in particular hypochloremic alkalosis and hypokalemia).

After all these possibilities have been ruled out, and errors disclosed and corrected, the administration of mercurial diuretics may be resumed or may be aided by the following measures:

1. Ammonium chloride[3] is given in doses of 3.0 to 4.0 gm. daily for 2 days prior to and on the day of the mercurial injections in order to supply the extra chloride needed to augment sodium excretion. The need for chloride medication develops particularly in case of prolonged severe dietary salt restriction. Ammonium chloride is best given in solution or in gelatine capsules since absorption from enteric coated tablets is uncertain.

2. Xanthine compounds may be used to advantage for the potentiation and prolongation of mercurial diuresis.[7] Theophylline increases cardiac output and renal blood flow but also reinforces the tubular depressant action of mercury. A tested three-day schedule is the following: On the first morning 2 cc. of a mercurial and 0.5 gm. of aminophylline (mixed in one syringe) are slowly administered by vein. The same dose of aminophylline alone is repeated (intravenously or intramuscularly) the same evening and every 8 to 12 hours on the following two days. This cycle may be repeated until the edema is removed. At this point the refractoriness to mercury often disappears and mercurials alone become again diuretically effective.

3. Decholin, 10 cc. of a 20 per cent solution of sodium dehydrochlorate, mixed with 2 cc. of a mercurial and slowly injected by vein, can also markedly increase mercurial diuresis.

4. The combination of Diamox®[2] with a mercurial may be indicated especially in cases of hypochloremia with waning diuresis. It seems that Diamox®, which promotes predominantly urinary sodium excretion, is capable of inducing diuresis even in the presence of chloride depletion. In cases of this type 0.25 to 0.5 gm. may be tried orally for a 5-day period, and the mercurial injected on the 3rd and 5th day.

5. Mechanical removal of retained body fluid by aspiration of transudates or the transcutaneous drainage of anasarca may occasionally restore the diuretic response to mercurials.

SUMMARY

1. Mercurial diuretics are indicated in the treatment of congestive heart failure whenever elimination of manifest or hidden fluid retention cannot be achieved by other means or cannot be obtained rapidly enough.

2. They are indicated also for therapeutic tests in differentiating left ventricular failure from other conditions with similar symptoms.

3. They are contraindicated in acute glomerulonephritis, in advanced renal failure, in electrolyte depletion, and in hypersensitivity to mercury. If an individual has shown hypersensitivity to some particular mercurial compound, further use of this preparation is contraindicated for this patient.

4. In spacing mercurial diuretics correctly, due consideration must be given to a possible delay in mercury excretion caused by renal impairment or scanty diuresis.

5. Serious side effects can be caused either by cumulation of mercury (mercurialism), by allergy to mercury or to a particular mercurial compound, or by excessive diuresis due to overdosage of the mercurial employed (electrolyte depletion, dehydration, spontaneous redigitalization, or acute urine retention).

6. Prolonged mercurial therapy should be guided by the diuretic results and possible side effects of each injection. It should not be based on routine schedules.

7. Intramuscular or subcutaneous injection is preferred to the intravenous route.

8. In refractory cases review of the diagnosis and the therapeutic management is suggested, and a combination of mercurials with diuretic agents with different mechanism of action is recommended. In cases of this kind an increase in dosage or frequency of mercurial injections is generally ineffective and often injurious.

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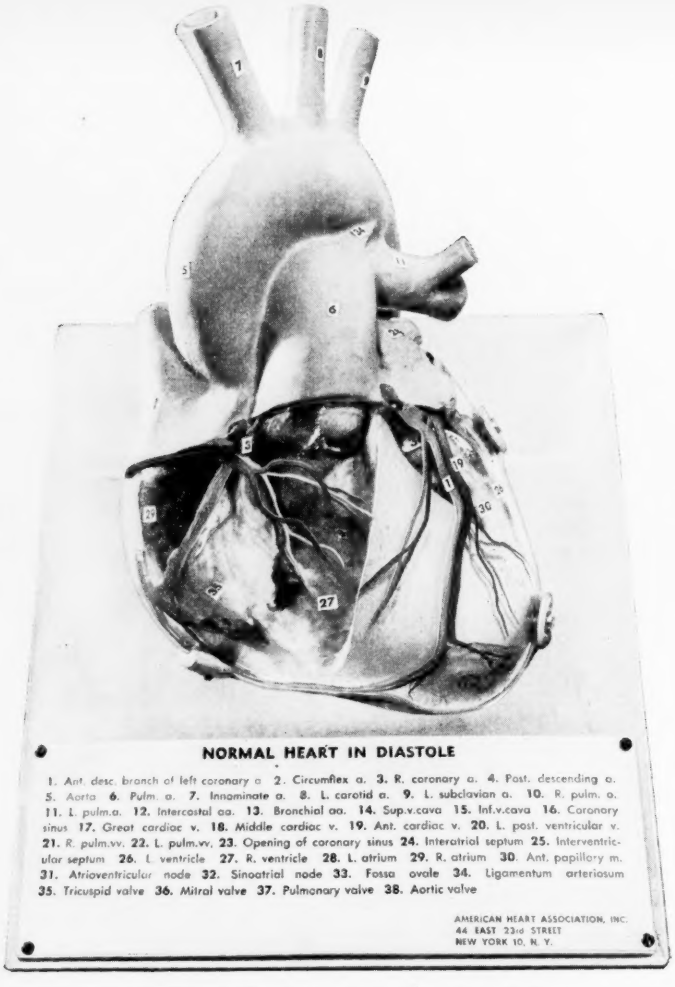
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